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Sulfur-assisted domino access to bicyclic dihydrofurans: case study and early synthetic applications†

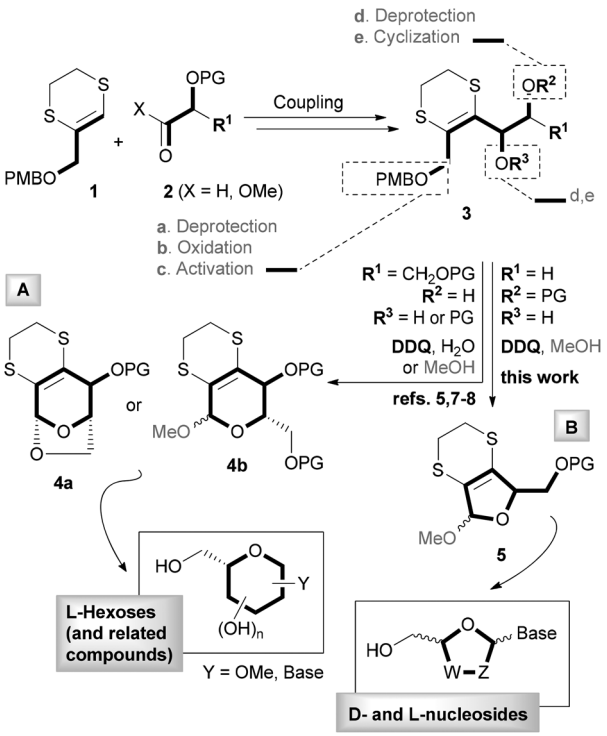
Concetta Paolella,‡ Daniele D'Alonzo,*‡ Giovanni Palumbo and Annalisa Guaragna*

A DDQ-mediated domino reaction (up to six steps in a single process) has been developed to selectively provide substituted dihydrofurans from a common starting material containing a cyclic bis-thioenol ether. Study of the reaction mechanism highlighted a role played by the sulfur-containing moiety in influencing reaction rate and stereoselectivity.

Rapid access to bioactive molecules is often hampered by time-consuming, costly protective group-based strategies and lengthy purification procedures after each synthetic step. To circumvent these inconveniences, the potential of multistep protocols, including domino reactions,[1] has been exploited for the efficient and elegant construction of even complex intermediates in a single process. In this context, our ongoing efforts working towards the *de novo* synthesis of optically active molecules of biological interest[2] led us to explore the potential of 1,2-bis-thioenol ether-containing systems[3] in undergoing domino reactions when used in combination with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ; Scheme 1). While use of heterocycle **1** brought on C_3-homologation of various electrophiles such as **2**, in many cases in a stereoselective fashion,[4,5] the versatile reactivity of DDQ – a result of its combined electron-transfer, oxidative and acidic properties[6] – enabled some new multistep cyclizations of the homologation products **3**, involving sequential 4-methoxybenzyl (PMB) group deprotection, oxidation of the resulting primary alcohol, formyl group activation, and eventual cyclization by a suitably unprotected hydroxyl function (Scheme 1).

Depending on further elaboration of the resulting sugar precursors, *e.g.* **4a** and **4b**, strategies leading to L-hexoses[5,7] and other structurally-related compounds[8] have already been developed (Scheme 1A). Along these lines, access to dihydrofurans **5** has been herein explored (Scheme 1B), mainly because of their potential application in the synthesis of bioactive D- and L-nucleosides[9] and nucleic acids.[2c] With this aim, we first looked at bicycle **9**, which was easily synthesized as depicted in Scheme 2. Coupling of **1** with glycolate **6** under known conditions[3] afforded ketone **7** in an 89% yield. After reduction[10] of **7** (BH_3·THF, 86%), reaction of the corresponding *sec*-alcohol **8** with DDQ (1.2 equiv.) in a 95/5 CH_2Cl_2–MeOH solution enabled direct conversion of the latter into an α/β mixture of methyl glycosides **9** (dr = 3.3 : 1; 83% yield) in only 30 min.

Surprisingly, minimal changes in the reaction conditions caused additional *in situ* transformations. Treatment of **8** with

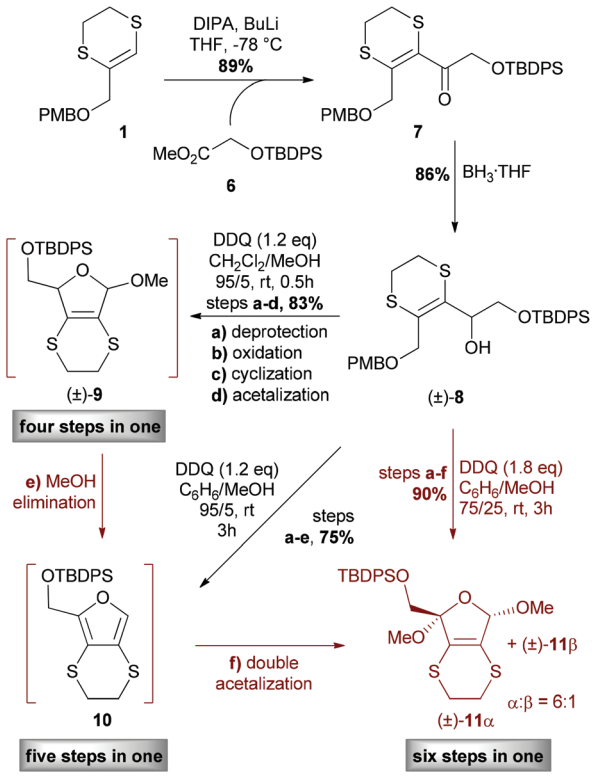


Scheme 1 *De novo* approach to synthetically useful sugar-like scaffolds **4** and **5**.

Dipartimento di Scienze Chimiche, Università degli Studi di Napoli Federico II, via Cintia 21, I-80126 Napoli, Italy. E-mail: dandalonzo@unina.it, guaragna@unina.it; Fax: +39 081 674393; Tel: +39 081 674119

†Electronic supplementary information (ESI) available: Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c3ob41324a

‡These authors contributed equally to this work.

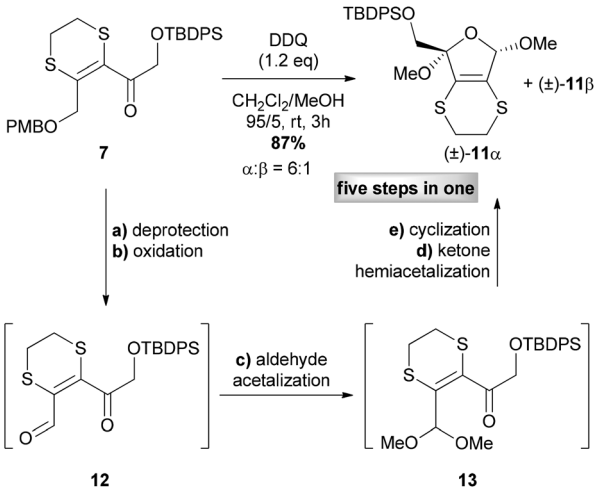


Scheme 2 Domino approach to (dihydro)furans **9–11**.

DDQ (1.8 equiv.) in a 75/25 C_6H_6–MeOH mixture led, after 3 h at rt, to formation of bis-acetal **11** (α : β = 6 : 1) in an excellent 90% yield (Scheme 2). As for **9**, the process can be considered a domino reaction, as it proceeded across six sequential steps, carried out in a single reaction vessel: (a) PMB group removal, (b) oxidation of the resulting primary alcohol, (c) ring closure, (d) acetalization, providing **9**, (e) MeOH elimination, leading to **10**, and (f) double acetalization. Notably, although furan **10** acted as an intermediate under these conditions, it could also be smoothly isolated as the main product (75%) from **8** by simply reducing the amounts of DDQ (1.2 equiv.) and MeOH (C_6H_6–MeOH = 95/5; Scheme 2).

Not fully unexpected, acetal **11** could be obtained in a single process even from ketone **7**, albeit by a different sequence of synthetic transformations (Scheme 3). Indeed, addition of DDQ (1.2 equiv.) to a 95/5 CH_2Cl_2–MeOH solution of **7** provided **11** (α : β = 6 : 1) after 3 h at rt in a very good 87% yield. Although none of the intermediates could be isolated, we reasonably assumed that formation of **11** was the result of five sequential steps, including oxidative deprotection of **7**, (hemi)acetalizations of **12** and **13** and subsequent cyclization of the latter[11] (Scheme 3).

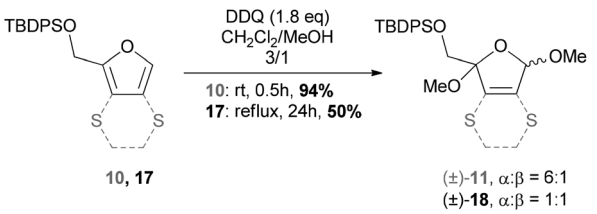
The unusual reactivity observed above apparently relies on a combination of the excellent synthetic versatility of DDQ and the intriguing chemical properties of the 1,4-dithiinyl group. Given the apparent synthetic potential of the process, its mechanism was investigated in greater detail.



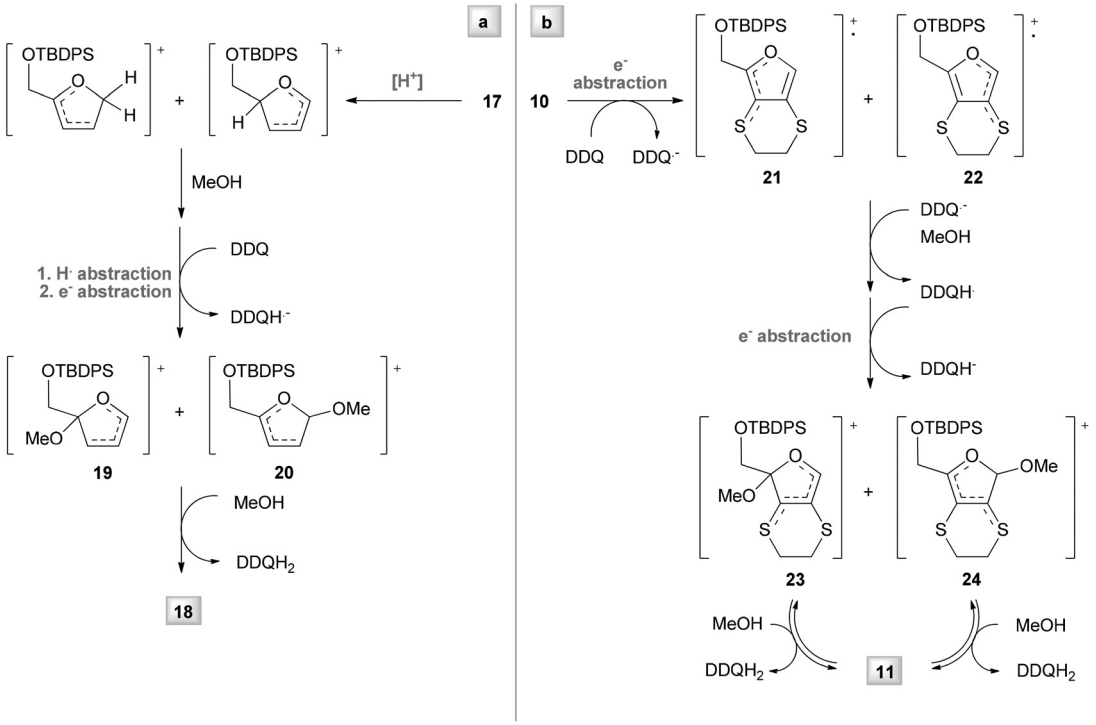
Scheme 3 Domino conversion of ketone **7** into acetals **11**.

We started by observing that the last transformation in Scheme 2 (step f) closely resembled the well-known Clauson-Kaas reaction, providing 2,5-disubstituted dihydrofurans from corresponding furans under electrochemical conditions[12] or by means of molecular bromine and chlorine.[13] Herein, we initially established that the same transformation could also be carried out by DDQ starting from furan **17** (Scheme 4). However, compared with the conversion of bicyclic furan **10** into **11**, the one leading to **18** from **17** was less efficient (50%), requiring harsher conditions (24 h at reflux) and resulting in no stereoselection (α : β = 1 : 1). Therefore, the crucial influence of the dithioethylene bridge on reaction rate and stereoselectivity became apparent.

We reasoned that acetalization of furan **17** involved a double MeOH addition under electron-transfer conditions, triggered by the *in situ*-originated[5,6,7b] acidic medium (Scheme 5a). Although bicycle **10** could in principle follow the same path, we more reasonably assumed that the latter underwent an early electron abstraction from one of the sulfur atoms, leading to formation of the radical cations **21** and **22** (Scheme 5b). A subsequent MeOH addition, followed by a further electron abstraction, then provided oxocarbenium ions (**23** and **24**). The stability of the species **21–24**, due to the wide positive charge delocalization by the sulfur atoms, could significantly contribute to accelerate the reaction. Along these lines, it's also conceivable that the stereochemical outcome of the process could be influenced by the thermodynamic equilibrium among **23**, **24** and **11** (apparently not occurring in the



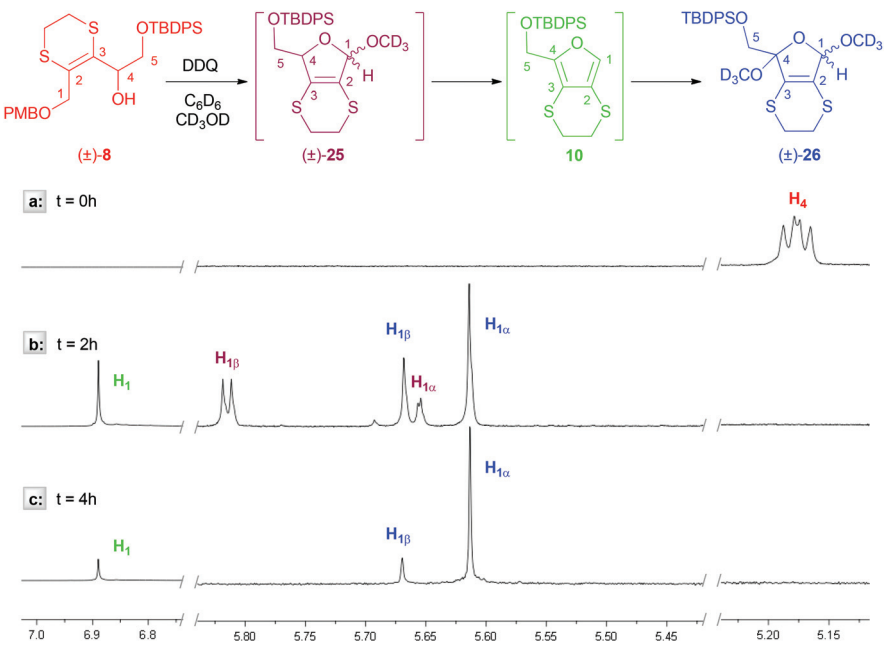
Scheme 4 DDQ-mediated double acetalization of **10** and **17**.



Scheme 5 DDQ-mediated double acetalization reactions: proposed mechanisms.

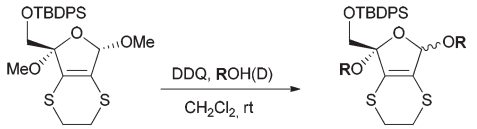
absence of the dithioethylene bridge, *i.e.* among **19**, **20**, and **18**) (Scheme 5).

In support of these assumptions, ^{1}H NMR monitoring of the domino reaction (performed in an NMR tube containing **8** and 1.8 equiv. of DDQ in a 3/1 C_6D_6–CD_3OD mixture) was carried out (Scheme 6). We excluded any mechanistic path other than that described in Scheme 2, by recognizing the disappearance of distinctive ^{1}H signals belonging to **8** [*e.g.* H_4 [14] (red) at 5.17 ppm, Scheme 6a] towards the sequential formation of those belonging to acetal **25** [$H_{1\alpha}$ and $H_{1\beta}$ (purple) at 5.66 ppm and 5.92 ppm, Scheme 6b], furan **10** [*e.g.* H_1 (green) at 6.89 ppm, Scheme 6b], and hence to bis-acetal **26** [$H_{1\alpha}$ and $H_{1\beta}$ (blue) at 5.62 ppm and 5.67 ppm, Scheme 6b and c]. Most importantly, the ongoing changes in the α/β ratio (*e.g.*,



Scheme 6 ^{1}H NMR monitoring of the domino reaction.

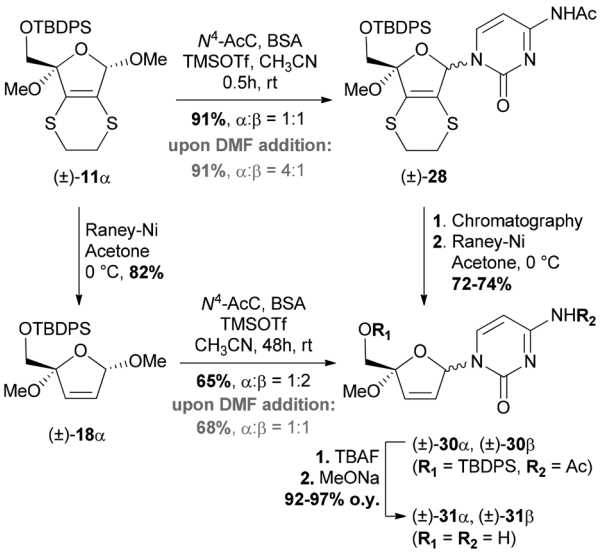
Table 1 DDQ-mediated double *trans*-acetalizations of **11**α[a]



(±)-**11**α (±)-**26,27a-c**

Entry	Compound	R	Time (h)	Yield (%)	(α : β)
1	**26**	CD_3[b]	24	>99[c]	6 : 1[c]
2	**27a**	CF_3CH_2	24	71	>20 : 1
3	**27b**	$HC{\equiv}CH_2$	48	83	6 : 1
4	**27c**	i-Pr	48	90	>20 : 1

[a] All reactions were carried out using large excesses of the acetalizing agents (≥10 equiv.). [b] $CDCl_3$ used in place of CH_2Cl_2. [c] Calculated by ^{1}H NMR of the crude reaction product.



Scheme 7 Synthesis of 4′-methoxycytidines **31**.

t = 2 h, α : β ~ 2 : 1; t = 4 h, α : β ~ 6 : 1; Scheme 6b and c) strikingly proved the equilibrium occurring between **26**α and **26**β.

Practical experimental evidence was also provided by treating anomerically pure **11**α with DDQ in a 3/1 $CDCl_3$–CD_3OD mixture (Table 1, entry 1); complete conversion (>99%) into **26** (α : β = 6 : 1) further confirmed the existence of an equilibrium between the two anomers. However, in our hands the same reaction did not proceed from desulfurized acetal **18**. This demonstrated that the thioenol ether moiety could activate neighboring acetal functions even under fairly mild acidic conditions. To test the scope of this activation path, DDQ-promoted double *trans*-acetalizations of **11**α using some readily available alcohols were also performed (Table 1, entries 2–4). After 24–48 h at rt, the corresponding bis-alk(yn)yl acetals **27a–c** were afforded in high yields (71–90%) and in good (**27b**, α : β = 6 : 1) to excellent (**27a**, **27c**, α : β > 20 : 1) diastereoselectivities.

It's worth noting that in the context of nucleoside chemistry[15] these acetalization products may represent a fruitful source of starting materials *en route* to biologically interesting 4′-substituted nucleosides.[16] As an early application, access to the 2′,3′-unsaturated 4′-methoxynucleosides **31**α and **31**β (cytosine being chosen as a model nucleobase)[17] was provided after sulfur bridge removal[18] from **11**α (RANEY®-Ni, 82%) and subsequent Vorbrüggen *N*-glycosidation of the resulting **18**α (TMSOTf, 65% yield, α : β = 1 : 2) (Scheme 7).[19] Alternatively, *N*-glycosidation was performed directly on **11**α, affording nucleoside **28** in a more convenient 91% yield (α : β = 1 : 1). A participating role by the sulfur bridge in anomeric centre activation was strongly suggested by the greatly shortened reaction times (30 min) compared with those of **18**α (48 h). Looking at anomeric stereoselectivity, while efforts to induce β-selectivity by *in situ* anomerization[8b] of **28** failed,[20] on the other hand we found an unprecedented role played by DMF[21] (6 equiv.) as an *N*-glycosidation modulator, inducing moderate α-selectivity in the formation of **28** (α : β = 4 : 1; Scheme 7). Notably, DMF was completely ineffective in driving the stereochemical outcome in the reaction leading to **30** (α : β = 1 : 1) from the desulfurized olefin **18**α. The α and β anomers of **28** were then separately subjected to desulfurization (RANEY®-Ni, 72–74%). Eventually, protective group removal from the olefin **30** (MeONa, then TBAF) released α- and β-2′,3′-dideoxy-2′,3′-didehydro-4′-methoxy-cytidine (**31**α and **31**β, 92–97% overall yield).

In summary, the study of the DDQ-mediated domino conversion of alcohol **8** into (dihydro)furans **9–11** has enabled to shed light on the peculiar reactivity profile of heterocycle **1**. Particularly, a key role played by the 1,4-dithiinyl moiety in the activation of the nearby acetal functions (influencing reaction rate and stereoselectivity) has been demonstrated by experimental evidence and NMR analysis. More generally, our results suggest that reactivity of acetal functions (including the anomeric centres of sugar precursors) can be remarkably increased by the presence of thioenol ether moieties. Preliminary examples involving *trans*-acetalization reactions under mild conditions (leading to bis-alk(yn)yl acetals **26–27**) and *N*-glycosidation reactions (leading to 4′-methoxycytidines **31**) have been performed. Further applications leading to the synthesis of other biologically interesting compounds are currently ongoing and will be published elsewhere.

Acknowledgements

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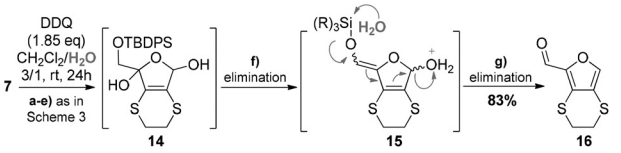
10 As we were interested to preliminarily explore the reactivity of our synthon **1** rather than to directly use it for medicinal chemistry applications, **8** was synthesized in racemic form. In some cases, the configuration of stereocentres is arbitrarily defined to display the relative stereochemistry of the newly formed stereocentres. Study of the synthetic conditions enabling preparation of **8** and/or that of the following intermediates in enantiopure form is ongoing.

11 Replacing MeOH with H_2O, an even more unexpected reactivity occurred, leading to furfural **16** (83%). Analogous to Scheme 3, the reaction was supposed to proceed through formation of bis-hemiacetal **14**, then undergoing H_3O^+-mediated double elimination. However, **16** was not stable enough for further synthetic manipulations.



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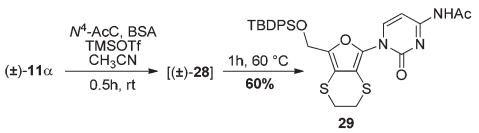
20 *N*-Glycosidation of **11**α at 60 °C provided furan **29** (formed *via* nucleoside **28**):



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